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Monocyte-to-HDL-cholesterol as a predictor of disease severity in acute pancreatitis

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ABSTRACT

Aims: Acute pancreatitis is an inflammatory process of the pancreas that can affect local tissues or distant organ systems. Recent studies have described the monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) as a significant prognostic marker. The aim of this study was to investigate the relationship between the MHR and disease severity in patients diagnosed with AP.

Methods: One hundred sixty-six AP patients were enrolled in this study. MHR and inflammatory parameters were measured for all study participants. Disease severity was measured using the Ranson score on admission, and cases were classified as mild or severe AP. MHR was then compared between the groups.

Results: MHR values were significantly higher in severe AP patients (25.2, range 7.89-77.8) compared with mild AP patients (14.32, range 0.71-80) (P=0.006). Based on the Ranson criteria, the overall accuracy of MHR in determining severe AP was sensitivity 72.7% and specificity 69% (AUC: 0.762; P=0.006). The overall accuracy of MHR in predicting disease severity was superior to other inflammatory markers.

Conclusion: The study findings indicated that MHR values are significantly elevated and capable of use in determining disease severity in AP patients.

Keywords: Monocyte, HDL, MHR, ranson, inflammation

INTRODUCTION

Acute pancreatitis (AP) constitutes an acute inflammatory process of the pancreas with variable involvement of local tissues or distant organ systems.[1,2] The clinical course is very wide, from self-limiting mild inflammation to severe organ failure.[3] Diagnosis can be easily established with acute onset typical abdominal pain and enzyme elevation (amylase and lipase). However, amylase and lipase elevations exhibit no correlation with disease severity, and their levels can also rise in some conditions other than AP (gastrointestinal perforation, salivary gland pathologies, kidney failure, etc.).[4]

The ability to predict the severity and prognosis of AP provides important clinical clues in the approach to the patient. Various scoring systems, such as Ranson, Glasgow, APACHE II and Balthazar, are therefore employed for this purpose.[5,6] A score of '0-2' on the Ransom scale, widely used in clinical practice among these different systems, predicts a risk of mortality below 3%, while scores of '3-4' predict a 15% risk of mortality.[7] Various studies have also suggested that some easily accessible, practical, and inexpensive markers can predict the severity of AP as an alternative to these scoring systems.[8-11] Two of these are the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR). Although it has been suggested that these two parameters can predict AP-related mortality and prognosis when used separately, the findings are inconsistent.

The monocyte count to high density lipoprotein (HDL) cholesterol ratio (MHR) has been described as a significant prognostic marker in recent studies. It has been reported that the ratio indicates the inflammatory process and disease exacerbation in many diseases such as cardiovascular diseases, obstructive sleep apnea syndrome, metabolic syndrome and acute intracranial hemorrhage.[12-16]

Furthermore, Paraoxonase-1 (PON1) is a HDL attached, extracellular esterase synthesized mainly in the liver. PON1 is believed to contribute to the anti-atherogenic and

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anti-inflammatory properties of HDL; it degrades lipid peroxides, decreases HDL susceptibility to peroxidation, glycation, and homocysteinylation, and increases cholesterol efflux from macrophages.[17] Franco-Pons et al.[18] have suggested that serum PON-1 undergoes inhibition and proteolysis during pancreatitis. In an another experimental study, Tvarijonaviciute et al.[19] have proposed that serum PON-1 activity is lower in dogs with AP.

However, despite the relationship between MHR and inflammation, the prognostic value of MHR in patients with AP has not previously been investigated. We think that MHR can represent an alternative to existing scoring systems in predicting the severity of AP.

The aim of this study was to investigate the relationship between MHR and AP severity in patients diagnosed with this condition.

METHODS

Ethics

The study was carried out with the permission of a Düzce University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 2022, Decision No: 64). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

One hundred sixty-six patients diagnosed with AP in our tertiary reference center in Turkey between April 2017 and January 2020 were included in this retrospective analysis. The diagnosis of AP was made with symptoms of severe typical abdominal pain, usually accompanied by vomiting, tenderness in the middle epigastrium, and serum amylase and lipase levels at least three times the upper threshold of normal.The diagnosis was also confirmed using transabdominal ultrasonography and computed tomography (CT). The etiology of AP, age, gender, medical history, radiological imaging and laboratory findings of the patients were taken from the medical files of the patients and all data were evaluated.

Individuals with conditions capable of causing pancreatic enzyme elevation other than AP (pancreatic cancer, chronic pancreatitis, gastrointestinal system perforations, and salivary gland diseases), or with chronic kidney failure, heart failure, liver failure, acute or chronic inflammation, cancer, or hematological disease, patients who take drugs that may affect lipid metabolism like thiazolidinedione, statin, and fibrates were excluded from the study.

Disease severity was measured using the Ranson score during admission. Five Ranson score variables were analyzed. Cases with scores <3 were classified as mild AP and those with scores ≥3 as severe AP.

The modified CT severity score (MCTSI) was developed based on the degree of necrosis and inflammation, and the presence of fluid collections. Under this system, a normal pancreas is scored 0, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat are scored 2, pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis are scored 4, the extent of pancreatic necrosis less than 30% is scored 2 and pancreatic necrosis exceeding 30% is also scored 4. The severity of pancreatitis was categorized as mild (0-3 points), moderate (4-6 points), or severe (7-10 points).

Laboratory analysis

Blood samples were collected by venipuncture with minimal stasis. All patients' blood specimens were collected during an initial presentation to the hospital. Fasting blood specimens for lipid profile analysis were collected the day after admission. Sera were separated by centrifugation at 4000 rpm for 10 minutes and then decanted. Routine parameters were evaluated photometrically at the Biochemistry Laboratory Research Hospital using an IDS B0728 auto analyzer device. Complete blood count analyses were performed using the same analyzer within 2 hours after collection of blood samples on a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer.

Statistical Analysis

The study data were analyzed on SPSS version 20.0 software (IBM Corp., USA). Quantitative parametric data were expressed as mean plus standard deviation (SD), and quantitative non-parametric data as median values plus minimum and maximum. The Kolmogorov–Smirnov test was used to analyze the distribution of variables. For non-parametric data, comparisons between different groups were performed using the Mann-Whitney U test, while the independent-t test was used to compare parametric data between the groups. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values for MHR and other inflammatory markers levels to identify AP severity with maximum sensitivity and specificity. p values below 0.05 were considered statistically significant.

RESULTS

One hundred sixty-six patients, 113 (70%) with biliary AP, and 53 (30%) with non-biliary AP were enrolled in the present study. Eighty-nine (53%) patients were men and 77 (47%) were women. The mean age of the patients was 62±19.6 years. There were no statistically significant differences between the groups in terms of clinical characteristics, laboratory values, or inflammatory markers (**Table 1**).

Table 1. Basic characteristics of patients with biliary and non-biliary acute pancreatitis

Parameters	Biliary Pancreatitis (n=113)	Non-biliary Pancreatitis (n=53)	P value
Age (year)	67±17	52±21	0.000
Gender (F/M)	48/65(42%/57%)	29/24(53%/46%)	0.264
WBC (mm³ ×10³)	10.5±4.5	10.6±3.7	0.952
Hemoglobin (g/dl)	13.7±1.7	14.2±1.2	0.972
Platelet (/mm³×10³)	214 (34-696)	203 (90-560)	0.613
Neutrophil (ml)	8.1±3.9	8.1±3.7	0.721
Lymphocyte (ml)	1.4±0.8	1.8±1.2	0.069
Monocyte (ml)	0.64 (0.03-8.5)	0.67 (0.27-1.54)	0.437
HDL (mg/dl)	45.8±18.3	46.7±19.5	0.810
LDL (mg/dl)	108±32	110±43	0.527
TG (mg/dl)	74 (33-170)	104 (41-412)	0.126
Urea (mg/dl)	37 (13-162)	29 (11-123)	0.847
Creatinine (mg/dl)	0.91 (0.16-591)	0.91 (0.44-6.91)	0.211
AST (U/L)	91 (19-1115)	44 (5-506)	0.000
Amylase (U/L)	846 (402-3141)	723 (404-3355)	0.304
Lipase (U/L)	1138 (28-1504)	849 (23-1469)	0.066
NLR	5.86 (0.16-31.4)	4.66 (0.33-27.1)	0.151
PLR	174 (26-1039)	119 (32-822)	0.059
MHR	14.4 (0.71-62.9)	16.1 (3.3-48)	0.792
Ranson, n(%)			0.146
0-3	102 (90)	41 (77)	
4-6	21 (10)	12 (23)	
MCTSI, n(%)	39	22	0.472
0-3	25 (50)	13 (59)	
4-6	10 (40)	7 (31)	
7-10	4 (10)	2 (10)	

WBC, white blood count; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MHR, monocyte HDL ratio; MCTSI, modified CT severity score.

WBC, NLR and MHR were significantly higher in the severe AP group than in the mild AP group (9.83±3.6 vs 13.9±5.9; 5.09 (0.16-31.4) vs 10.28 (2.1-31); and 14.32 (0.71-80) vs 25.2 (7.89-77.8), respectively p<0.005 for all). No difference was observed between the two groups in terms of monocyte or HDL parameters (p>0.05), MHR differed significantly between the two (Figure 1).

ROC curve analysis suggested that the optimum MHR level cut-off point for severe AP based on Ranson scores was 18.6, with sensitivity, specificity of 76%, 69%, respectively (AUC: 0.716; p=.006). The same ROC curve analysis for MHR and other inflammatory markers is also shown in Table 3 and Figure 2.

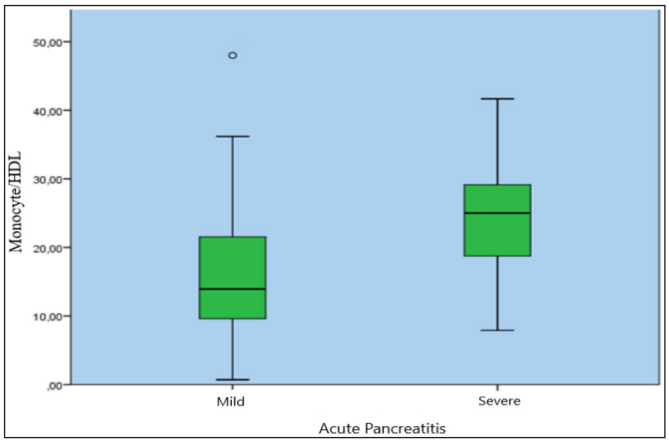

Figure 1. MHR levels between mild and severe pancreatitis

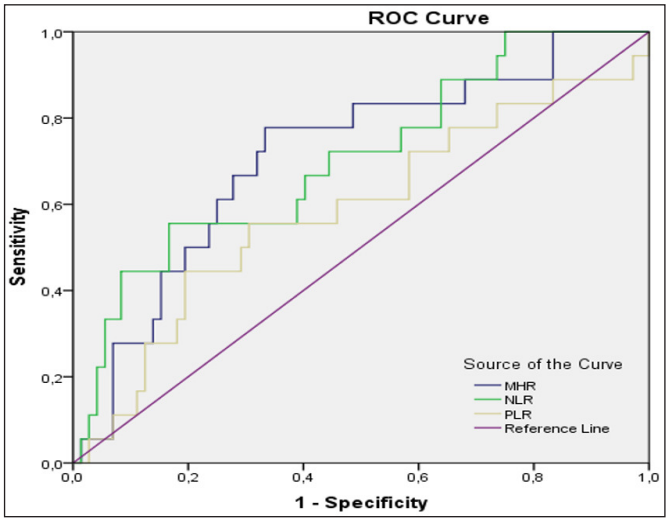

Figure 2. Overall accuracy and ROC analyses of MHR and other inflammatory markers in differentiating mild from severe AP according to the Ranson criteria

Table 2. A comparison of inflammation parameters in terms of severity of acute pancreatitis

Parameters	Mild pancreatitis (n=143)	Severe pancreatitis (n=33)	P value
WBC	9.83±3.6	13.9±5.9	0.003
Neutrophil (ml)	7.54±3.1	11.1±4.7	0.002
Lymphocyte (ml)	1.65±0.1	1.26±0.8	0.088
MCV	87±6	87±7	0.913
MPV	9±2	10±2	0.237
Monocyte (ml)	0.64 (0.30-8.5)	0.72 (0.2-4.67)	0.216
HDL	47.4±19.3	38.8±16	0.083
NLR	5.09 (0.16-31.4)	10.28 (2.1-31)	0.001
PLR	145 (31.4-1039)	220 (25-836)	0.065
MHR	14.32 (0.71-80)	25.2 (7.89-77.8)	0.006
CRP	7.3 (0.5-85)	10.2 (0.2—289)	0.134

WBC, white blood count; MCV, mean corpuscular volume; MPV, mean platelet volume; HDL, high density lipoprotein; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MHR, monocyte HDL ratio.

Table 3: Overall accuracy and ROC analyses of MHR and other inflammatory markers in differentiating mild from severe AP according to the Ranson criteri

Parameters	AUC	Cut-Off	Sensitivity %	Specificity %	95% CI		p value
MHR	.716	18.6	76	69	.579	.006	.853
NLR	.691	5.66	64	60	.550	.015	.831
PLR	.570	119	64	42	.407	.374	.732

DISCUSSION

MHR was higher in severe AP than in mild AP in the present study. In addition, it was superior to previously investigated inflammatory markers such as NLR, PLR, and CRP in predicting the the severity of AP. To our knowledge, this is the first study to investigate MHR in predicting AP severity.

AP is an acute inflammatory disease arising from gallstone disease and capable of leading to significant morbidity and mortality. Although it is generally well-tolerated and self-limiting, it may sometimes be fatal due to the development of multi-organ failure.[20] Being able to predict the severity of AP might make it possible to reduce morbidity and mortality rates by modifying therapeutic and follow-up approaches. However, there is currently no ideal marker capable of predicting the severity of the disease.

CRP, an inflammatory marker frequently used alone, is not sufficiently capable of predicting the severity of AP. This is because the fact that it rises at least 24-48 h after the onset of symptoms and pancreatic inflammation limits its use in predicting AP severity.[21] Similarly in the present study, no statistically significant difference was observed in CRP values at the time of presentation between mild and severe AP.

The fact that NLR is characterized by a significant increase in inflammatory conditions has recently encouraged its clinical use. One recent study identified NLR as an independent predictor for the diagnosis of coronavirus 2019 (COVID-19).[22] Another study identified a link between NLR and malignancies.[23] NLR has also been shown to be useful as a prognostic factor in patients with AP.[24] A significant positive correlation was also found between NLR and Ranson score in another study.[25]

PLR, another of the parameters related to inflammation, has also been associated with the severity of AP and AP-related mortality Zhou et al.[10] Kaplan et al.[9] identified PLR as a significant predictor of prognosis in AP. Consistent with the previous literature, a significant relationship was determined between PLR and the severity of AP in the present study.

Recent publications have shown a particular association between MHR and cardiovascular events.[15,26] Monocytes and macrophages play an important role in atherosclerotic plaque formation. Monocyte count has been identified as an independent predictor of subsequent plaque formation.[27] In addition, proinflammatory cytokines such as interleukin (IL)-6, IL-1β and tumor necrosis factor-α (TNFα) are released from monocytes during the inflammatory process.[28] The monocyte count in peripheral blood increases in AP.[29] Increased monocyte activation has also been observed in mice with experimentally induced AP.[30]

The most important mission of high-density lipoprotein-cholesterol (HDL-C) is to transport cholesterol from cells and tissues to the liver. However, it also exhibits anti-atherosclerotic properties by eliminating the proinflammatory and pro-oxidant effects of monocytes through the inhibition of macrophage migration and LDL oxidation.[31] HDL has been shown to exhibit a negative response in the course of AP.[32] In light of the above, an increasing monocyte count and decreased HDL are thought to be capable of use as a marker in inflammatory conditions. One study recently investigated the value of the HDL/LDL ratio in predicting the severity of AP Wu et al.[33], and concluded that the ratio was significant in predicting the progression of the disease. An AUC of 0.533 was determined in that study at ROC analysis of the HDL/LDL ratio based on Ranson criteria used to calculate the severity of AP. The AUC for MHR in the present study was 0.716 (p=0.006).

The principal limitations of this study are its retrospective cross-sectional design, single center experience, and the low number of patients. Other limitations include the absence of other scoring systems used in predicting the severity of AP, other than the Ranson score, and the lack of follow-up data.

CONCLUSION

The present study demonstrated for the first time significantly elevated MHR levels capable of determining disease severity in AP patients. We, therefore, think that MHR is a valuable tool for providing a rapid overview as a simple and inexpensive test in the evaluation of AP disease activity and that the present research can serve as a guide for future prospective studies with larger patient numbers..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of a Düzce University Medical Faculty Non-interventional Clinical Researches Ethics Committee (Date: 2022, Decision No: 64).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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